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The Acute Effect of Piretanide upon Serum and Urinary Calcium in Normal Subjects

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We gave piretanide, a new diuretic, at two dose levels to six normal subjects. Sodium excretion increased six to eightfold in the first two hours, and diuresis was completed within four hours. There was a simultaneous increase in the excretion of calcium which exceeded the amount present in the mobilized extracellular fluid. The resulting deficit of calcium produced a small but significant fall in serum calcium corrected for protein. After diuresis ended, calcium was retained but not sodium, when compared to basal values on the previous day. The fall in urinary calcium and the failure to correct the sodium deficit may both have resulted from increased secretion of parathyroid hormone (PTH), which increases calcium reabsorption and decreases sodium reabsorption. The role of PTH in the long-term effects of diuretics on sodium and calcium excretion requires further study.

Potent diuretics such as thiazides, furosemide, and ethacrynic acid have a marked effect on calcium metabolism. Thiazides produce a significant fall in urinary calcium excretion (1-3) and, in some circumstances, a rise in serum calcium (4-8); the mechanism of these effects has been extensively studied (9-12). Furosemide, on the other hand, induces a prompt rise in calcium excretion (13-15), which is blunted during prolonged administration (16). During furosemide treatment, serum calcium does not change in patients with initially normal levels (17). We report the acute effect of two different dose levels of piretanide (3-Pyrrolidine-4-phenoxy-5-sulfamoybenozoic acid), a new, high-ceiling diuretic with a sulfonamide structure (18), on serum and urinary calcium and phosphate in normal men.

Materials and Methods

The age, sex, weight, and blood pressure of the six normal volunteers are shown in Table 1. The subjects were studied during three consecutive days: Day 1 was a control; on Day 2, 3 mg of piretanide was given orally at 10 a.m.; on Day 3, 6 mg of piretanide was given orally at 10 a.m. To assure an adequate urine volume, the volunteers drank 500 ml of water at 8 a.m., and 250 ml at 10 a.m., 12 noon, and 2 p.m. During the two days before the study and on the three test days, the subjects ate their usual home diets; but to avoid large dietary changes in sodium or calcium intake, the following items were not allowed: milk and all dairy products except butter, and all foods with a high sodium content such as broth, crackers, and cold cuts.

On each day, urine was collected during the following periods: 8-10 a.m., 10 a.m.-12 noon; 12-2 p.m., 2-4 p.m., and 4-8 a.m. on the next day. Blood samples were obtained each day at 9 a.m. and 1 p.m. Sodium, calcium, phosphate, and creatinine were measured on each sample of urine, and calcium, phosphate, creatinine and total protein were measured on each sample of serum, using previously published methods (19). Serum calcium was corrected for protein according to the formula: Corrected Ca= measured Ca/(0.6 + total proteins/18.5). This formula assumes that the total calcium is 60% ultrafiltrable and that the protein-bound fraction changes in proportion to total protein (4).

TABLE I

Age, Sex, Weight, Height and Blood Pressure of Six Normal Volunteers

Patient	Age	Sex	Weight (kg)	Height (cm)	Basal Blood pressure (mmHg)
1	42	M	77.5	177	110/70
2	23	F	66.4	167	120/80
3	37	F	63.5	164	110/80
4	20	M	61.1	180	110/70
5	31	F	60.7	170	110/60
6	22	F	47.7	152	115/70

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TABLE II

Effect of Oral Administration of Piretanide at 10 a.m. Upon Urinary Volume, Sodium, and Calcium Excretion*

	Before Piretanide	After Piretanide			Diuretic Period	Postdiuretic Period	Total 24 Hrs
	8-10 a.m.	10 a.m.-12 noon	12 noon-2 p.m.	2-4 p.m.	10 a.m.-2 p.m.	2 p.m.-8 a.m.	
Basal	279±51	344±69	266±58	177±29	610±97	973±101	1861±1561
Piretanide 3mg	217±69	699±173[5]	317±102	171±50	1016±165	922±128	2155±342
Piretanide 6mg	163±47	1001±150[6]	321±83	110±49	1322±105[3]	597±94	2083±141
Basal	11±3	11±3	11±2	8±3	22±5	56±9	90±14
Piretanide 3mg	7±2	57±18[4]	32±13	11±2	89±15[3]	52±11	149±22[1]
Piretanide 6mg	6±1	84±16[6]	25±8(D)	12±9	109±10[3]	50±13	164±18[1]
Basal	13±3	10±1	10±1	9±2	20±1	93±19	126±20
Piretanide 3mg	10±2	40±10[4]	22±8	10±2	62±10[2]	57±7[1]	128±13
Piretanide 6mg	10±2	55±9[6]	21±3[4]	6±2	76±6[3]	51±25	136±26

[1] $p < 0.05$ compared to basal period
[2] $p < 0.01$ compared to basal period
[3] $p < 0.001$ compared to basal period
[4] $p < 0.05$ compared to 8-10 a.m. period
[5] $p < 0.01$ compared to 8-10 a.m. period
[6] $p < 0.001$ compared to 8-10 a.m. period
* Results are average ± SEM.

Results

After both doses of piretanide had been given, the increases in sodium, water, and calcium excretion were rapid in onset and were completed in four hours (Table II). As well as values for individual periods, the Table also shows cumulative values for the duration of the diuresis (10 a.m.-2 p.m) and for the remainder of the study period (2 a.m.-8 a.m.). After diuresis subsided, there was no fall in sodium excretion despite a persistent sodium deficit, but there was a significant fall in calcium excretion compared to the control day (Table II), so that total 24-hour urinary calcium was not increased. The different effects of piretanide on sodium and calcium are compared in Fig. 1. Fig. 2 shows the individual values for calcium excretion during the postdiuretic period (4 a.m.-8 a.m.).

One subject with a relatively high basal excretion showed a decrease after 3 mg of piretanide but a return to basal levels with the 6 mg dose. Meanwhile, all other subjects showed a significant diminution.

No changes were observed in total serum calcium after piretanide administration (Table III). However, the serum protein level rose so that corrected serum calcium was significantly lower at the time of peak action of the diuretic. No changes were observed in the serum levels of phosphate. Although the urinary excretion of phosphate rose in some subjects, this effect was inconsistent and the mean changes in urinary phosphate excretion, renal phosphate clearance, and renal tubular reabsorption of phosphate were not significant.

The administration of piretanide did not induce a significant change in serum or urinary creatinine levels, but the creatinine clearance during the 10 a.m. -2 p.m. period was lower after the 6 mg dose (basal: 91 ± 7 ml/m; piretanide 3 mg:88 ± 9 ml/m; piretanide 6 mg:81 ± 8; $P<0.005$ as compared to basal period).

Piretanide produced some decrease in body weight but no change in blood pressure. Transient side effects consisting mainly of headache, dizziness, and uneasiness were observed with the 6 mg dose.

Discussion

The urinary excretion of calcium depends on glomerular filtration and subsequent tubular reabsorption. Approximately 70% of the filtered load is reabsorbed in the proximal convoluted tubule and 20% in the ascending limb of Henle's loop. At both sites the reabsorption of calcium follows closely the reabsorption of sodium. Finally, 6 to 9% of the filtered calcium is reabsorbed in the distal tubule and collecting duct by mechanisms independent of sodium reabsorption, but probably under hormonal control, especially parathyroid hormone (PTH) secretion. Piretanide, a

TABLE III

Serum Calcium Levels 3 Hrs After Piretanide Administration

	Basal day	Piretanide 3 mg	Piretanide 6 mg
Total serum calcium (mg/dl)	9.4±0.2	9.4±0.2	9.5±0.2
Total proteins (g/dl)	7.6±0.2	7.8±0.2	8.0±0.1
Corrected serum calcium (mg/dl)	9.33±0.23	9.18±0.2*	9.17±0.21*

* $p < 0.05$ student's test for paired samples

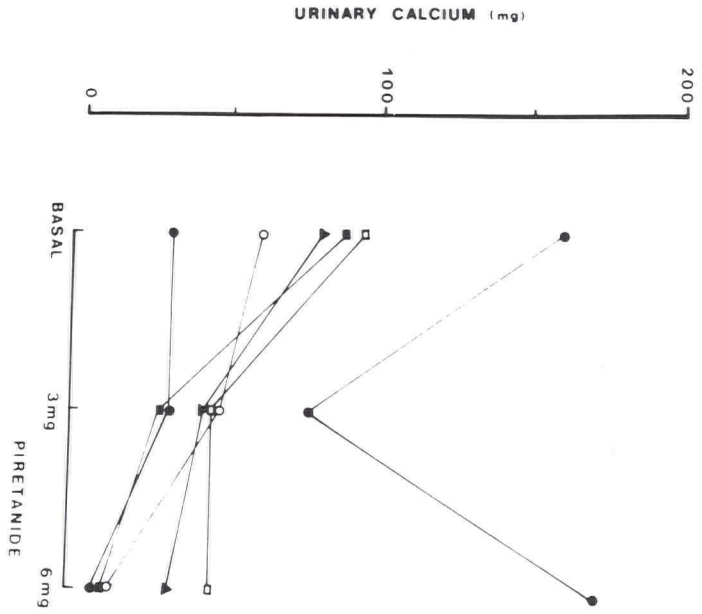

Fig. 1

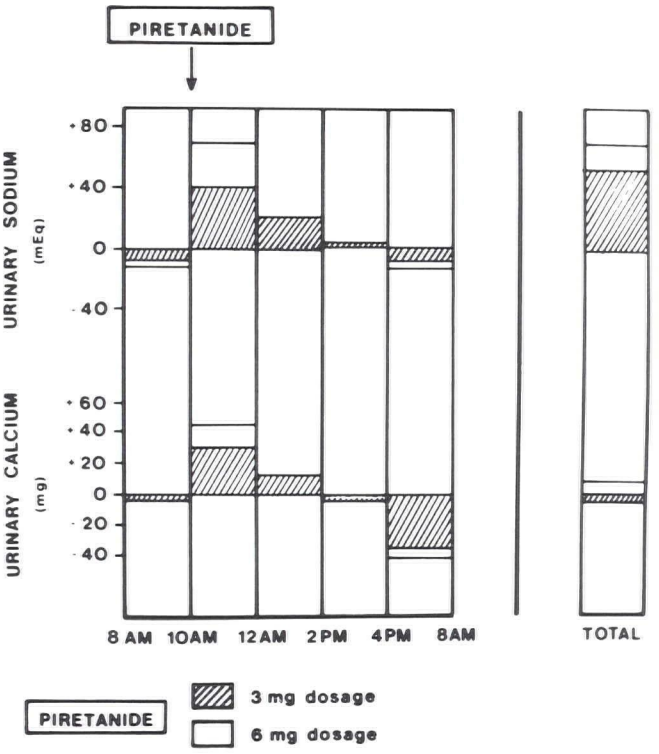

Fig. 2

new diuretic with structural similarities to bumetanide and furosemide, is a natriuretic agent that has an important inhibitory action on sodium and chloride transport in the ascending portion of the loop of Henle (20).

In the present study we observed a prompt increase of sodium and calcium excretion but no changes in urinary phosphate after the oral administration of piretanide. Similar observations have been reported by Teredesai and Puschett (20), who studied urinary electrolyte excretion during the peak natriuretic period after the intravenous administration of piretanide. The increased excretion of calcium observed in the present study was most likely the result of decreased reabsorption of sodium or chloride, induced by the administration of piretanide. However, the calcium loss was disproportionate to the increment observed in urinary sodium.

The loss of 66 mEq (3 mg dose) and 87 mEq (6 mg dose) of sodium (Table IV) with an osmotically equivalent amount of water would reduce both plasma and extracellular fluid (ECF) volumes by 470 and 620 ml, respectively, assuming a serum sodium concentration of 140 mEq/1. These volumes of ECF would contain 27 and 35 mg of calcium, respectively, assuming that ultrafiltrable calcium was 60% of total calcium. With both doses of piretanide, the observed increases in calcium excretion were greater than could be accounted for by mobilization of ECF. The differences of 15 mg and 21 mg represent deficits which, if evenly distributed over an ECF volume of 14 liters, would reduce the calcium concentration by 0.11 and 0.15 mg/dl, respectively. These predicted changes are very close to the decreases in corrected serum calcium which we observed (Table IV).

Whatever the mechanism, the fall in corrected calcium, and presumably also in ionized calcium, would be expected to increase the secretion of PTH. This hormone increases the tubular reabsorption of calcium (21), so that increased PTH secretion is a likely explanation for the fall in calcium excretion which occured during the evening and night after piretanide had been administered. The acute administration of PTH also increases the urinary excretion of sodium (21), so that increased PTH secretion may be one reason for the failure of sodium excretion to drop after diuresis ends, as would be expected in response to a sodium deficit. After the 3 mg dose of piretanide, the deficit was still uncorrected when the 6 mg dose was given, so that its effect may have been slightly blunted.

It is interesting to compare the response to piretanide with the response to mercurial diuretics. The latter produce an increase in calcium and sodium excretion in the same proportion as their ECF concentrations and no decline in corrected plasma calcium; but after diuresis subsides, there is substantial retention of both sodium and calcium (22). This suggests that there are two different mechanisms for increased calcium reabsorption and fall in calcium excretion after an acute diuresis. If the loss of calcium is disproportionate to the loss of sodium, there is a fall in ionized calcium and increased secretion of PTH. Conversely, if the loss of calcium is proportionate to the loss of sodium, there

TABLE IV

Relationship Between Changes in Plasma and Urinary Calcium after Piretanide

		Piretanide 3 mg	Piretanide 6 mg
Change in sodium excretion* (mEq)		+66	+87
Change in calcium excretion (mg)	observed*	+42	+56
	expected**	+27	+35
	difference	+15	+21
Change in calcium concentration (mg/dl)	observed	−0.15	−0.16
	expected***	−0.11	−0.15

*Changes in sodium and calcium excretion are differences between basal and experimental days from 10 a.m. to 2 p.m.

**Calcium contained in the mobilized ECF, assuming that sodium concentration was 140 mEq/1 and that ultrafiltrable calcium was 60% of total calcium.

***Assuming that calcium lost in excess of amount contained in mobilized ECF is distributed in the remaining ECF volume of 14 liters.

will be no change in ionized calcium or PTH secretion, but increased sodium reabsorption in response to volume contraction.

In some respects, the action of piretanide resembles the action of furosemide. When given to patients with partial parathyroid insufficiency, this diuretic induced a significant drop in ionized calcium, an increase in PTH secretion (in spite of the partial surgical hypoparathyroidism), and markedly augmented urinary calcium excretion (23). The failure to limit the increase in calcium excretion may have resulted from a suboptimal PTH response to the fall in ionized calcium. In normal subjects, furosemide increases urinary calcium excretion significantly in the first eight hours (15), but then with continued administration, it returns to base line levels (16). This is the expected result of a return of sodium excretion to the pretreatment level, an adaptive response probably mediated by increased sodium reabsorption in the proximal tubule and loop of Henle, in response to volume contraction. Absence of a steady state change in sodium excretion is characteristic of all diuretics and is accompanied by a parallel lack of steady change in calcium excretion, with the exception of thiazide diuretics, which produce a sustained fall in urinary calcium. Further studies are needed to determine the relative importance of increased PTH secretion and sodium adaptation in modifying the long-term effects of piretanide and other diuretics on the urinary excretion of calcium.

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